Remarks/Arguments

Claims 119-126 and 129-131 are pending in this application. Claims 119-124 have been amended. No new matter has been added.

I. 35 U.S.C. §§ 101 and 112, First Paragraph –Utility/Enablement

Claims 119-126 and 129-131 stand rejected under 35 U.S.C. §101 and §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action, one skilled in the art clearly would not know how to use the claimed invention." (Pages 2-3 of the instant Final Office Action)

Applicants strongly disagree and, therefore, respectfully traverse the rejection.

Applicants submit that the data presented in Example 170 starting on page 539 of the specification, and the cumulative evidence of record, indeed support a "specific, substantial and credible" asserted utility for the presently claimed invention. Applicants rely upon the gene amplification data of the PRO1153 gene for patentable utility of the claimed PRO1153 polypeptides. This data is clearly disclosed in the instant specification in Example 170, which discloses that the gene encoding PRO1153 showed significant amplification in primary lung tumors. As disclosed in previous response on record, Applicants submit that one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly over expressed and has utility in the diagnosis of lung cancers or for individuals at risk for developing lung cancer.

The Examiner asserts that basis of the rejections is solely that gene amplification levels are not predictive of mRNA or polypeptide levels. (Page 3 of the instant Final Office Action).

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, Applicants have submitted, in their Supplemental Amendment filed August 4, 2005, a Declaration by Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker

for the diagnosis of lung cancers, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Second, Applicants have submitted, in their Response filed June 25, 2004, ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For instance, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* collectively teach that in general, gene amplification increases mRNA expression. Third, Applicants have submitted over a hundred references, along with Declarations of Dr. Paul Polakis, which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is generally a positive correlation between DNA, mRNA, and polypeptide levels, in general, in the majority of amplified genes, the art overwhelmingly shows that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly overexpressed and has utility in the diagnosis of lung cancers.

Applicants further submit that, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin (both made of record in Applicants' Response filed June 25, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu. Therefore, as a general rule, one skilled in the art would find it more likely than not that PRO1153 polypeptides are useful as a diagnostic tools for detecting lung tumors.

Accordingly, Applicants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed PRO1153 polypeptides.

The Examiner has asserted that "lung cells can be aneuploid without the presence of cancer" and cites references by Hittelman et al. and Sen et al. in support of the assertion that " it is not clear that PRO1153 is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium." (Page 4 of the instant Final Office Action).

Applicants submit that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. As explained by Dr. Ashkenazi in his Declaration (submitted with Applicants' Response filed June 25, 2004),

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

Regarding Sen and Hittelman, Applicants agree that while aneuploidy can be a feature of damaged tissue as well, besides cancerous or pre-cancerous tissue, and may not invariably lead to cancer, Sen *et al.* in fact support the Applicants' position that PRO1153 is still useful in diagnosing pre-cancerous lesions or cancer itself. For instance, the art in lung cancer at the time of filing of the instant application clearly described that "epithelial tumors develop through a multistep process driven by genetic instability" in damaged lung lesions which may eventually lead to lung cancer. Many articles published around the effective filing date of this application studied such damaged or premalignant lesions and suggested that identification of such pre-cancerous lesions were very important in preventive diagnosis and treatment of lung cancer. Based on the well-known art, Applicants submit that there is utility in identifying genetic biomarkers in epithelial tissues at cancer risk.

The Examiner has asserted that significant further research is would have been required of the skilled artisan to reasonable confirm that PRO1153 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent, thus the asserted utility is not substantial. (Page 9 of the instant Final Office Action).

As discussed in previous responses of record, M.P.E.P. §2107.01 cautions Office personnel not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather,

any reasonable use that an Applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[1] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[2] gives the following instruction to patent examiners: "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Applicants' position is based on the overwhelming evidence from gene amplification data disclosed in the specification which clearly indicate that the gene encoding PRO1153 is significantly amplified in certain lung tumors. Based on the working hypothesis among those skilled in the art that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, one skilled in the art would simply accept that since the PRO1153 gene is amplified, the PRO1153 polypeptide would be more likely than not over-expressed. Thus, data relating to PRO1153 polypeptide expression may be used for the same diagnostic and prognostic purposes as data relating to PRO1153 gene expression. Therefore, based on the disclosure in the specification, no further research would be necessary to determine how to use the claimed antibodies to the PRO1153 polypeptide, because the current invention is fully enabled by the disclosure of the present application.

Accordingly, Applicants submit that based on the general knowledge in the art at the time the invention was made and the teachings in the specification, the specification provides clear guidance as to how to interpret and use the data relating to PRO1153 polypeptide expression and that the claimed PRO1153 polypeptide have utility in the diagnosis of cancer.

The Examiner asserts that "the instant disclosure does not show reliable fluorescence of PRO1153 even within the same experimental group. In addition, the instant Specification does not provide proper statistical analysis such as reproducibility, standard error rates, etc." (Page 6 of the instant Final Office Action).

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[1] M.P.E.P. §2107.01.

[2] M.P.E.P. §2107 II(B)(1).

Applicants submit that the Examiner is applying a standard that is not legally correct. The law, as it is reflected in the M.P.E.P. and the Utility Guidelines does not require that the Applicant show a positive result in a statistically large percentage of the tissue samples studied in order to make an assertion of utility. The above remarks by the Examiner are a clear indication that the Examiner applies a standard that might be appropriate, if the issue at hand were the regulatory approval of a diagnostic assay based on the overexpression of PRO1153 in lung tumor, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA reviewing an application for a new diagnostic assay will indeed ask for actual numerical data, statistical analysis, and other specific information before a diagnostic assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards for market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States. *Scott* v. *Finney,* 34 F.3d 1058, 1063,32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson* v. *Bowler,* 626 F.2d 853,856,206 USPQ 881, 883 (CCPA 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to a diagnostic utility as well. The identification of a diagnostic utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

Further, the Goddard Declaration was presented to show what delta Ct values were considered significant in the TaqMan" assay. The deltaCt values for PR01153 of at least 1.01-1.52 deletaCt units which corresponds to $2^{1.01}$ -$2^{1.52}$ -fold amplification or 2.013-fold to 2.868 -fold amplification in adenocarcinomas or squamous cell carcinomas of the lung, were considered significant according to the Goddard declaration. The formula for showing how the data was analyzed has been clearly disclosed in the specification in Example 170, page 539. As explained in the passage on page 539, lines 37-39, "the results of TaqMk™ PCR are reported in ~Ct units. One unit corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Table 9C indicates that PRO1153 showed approximately 1.01-1.52 deltaCt units which corresponds to $2^{1.01}$ -$2^{1.52}$ -fold amplification or 2.013-fold to 2.868 -fold amplification in adenocarcinomas or squamous cell carcinomas of the lung.

The Examiner has further asserted that " Only about 6% of the experimental samples tested positive, even within each tumor type and subtype." (Page 8 of the instant Final Office Action)

Applicants respectfully point out that they have shown significant DNA amplification in two different adenocarcinomas and squamous cell carcinomas of the lung. The fact that not all lung tumors tested positive in this study does not make the gene amplification data less significant. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even with most tumors. For example, the article by Hanna and Mornin (submitted with the Response filed June 25, 2004), discloses that the known breast cancer marker HER-2/neu is "amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma" (page 1, col. 1).

Applicants submit that the amplification of the PRO1153 nucleic acids in even one lung tumor provides specific and substantial utility for the nucleic acid as a diagnostic marker of the type of lung tumor in which it was amplified. Applicants further note that the tumors listed in Table 8 are not similar tumors from different patients, but various types/classes of lung and/or colon tumors at different stages. Accordingly, a positive result from one tumor, where the nucleic acid was amplified, but not from other tumors, indicates that the nucleic acid can be used as a marker for diagnosing the presence of that kind of tumor in which it was amplified. Amplification of the nucleic acid would be indicative of that specific class of lung or colon tumor, whereas absence of amplification would be non-conclusive. The skilled artisan would certainly know that such tumor markers are useful for better classification of tumors. Therefore, whether the PRO1153 gene is amplified in two lung tumors or in all lung tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, the fact that the amplification data for PRO1153 is considered significant is what lends support to its usefulness as a tumor marker. If the goal is to diagnose lung cancer, then contrary to the Examiner's assertion, a positive result does indicate the presence of cancer, while a negative result is not conclusive, and requires follow up testing.

The Examiner is also apparently concerned that no mutation or translocation of PRO1153 has been associated with a cancer. The Examiner further asserts "there is no disclosure regarding what treatment modality should be chosen by the clinician based on

whether or not the PRO1153 gene is overexpressed." (pages 7-9 of the instant Final Office Action).

However, knowledge of a mechanism of action is not required to discover the utility of a cancer diagnostic. Applicants note that overexpression of cancer markers is presently used in the diagnosis of, and in guiding the treatment of, cancer patients (see, e.g., Hanna and Mornin, of record).

Applicants further cite Hyman *et al.* ("Impact of DNA Amplification on Gene Expression Patterns in Breast Cancer," *Cancer Research* 62:6240-6245 (2002), of record), which discloses studies of gene amplification. One of the genes found to be amplified, HOXB7, was found to show "a clinical association between HOXB7 amplification and poor patient prognosis." (Page 6244, col.1 to col.2). Thus the results of Hyman *et al.* confirm that genes which are amplified in tumors have prognostic utility. Applicants also cite Pollack *et al.* ("Microarray Analysis Reveals a Major Direct Role of DNA Copy Number Alteration in the Transcriptional Program of Human Breast Tumors," *Proc. Natl. Acad. Sci. USA* 99:12963-12968 (2002), of record), wherein these authors conclude that "a substantial portion of the phenotypic uniqueness (and, by extension, the heterogeneity in clinical behavior) among patients' tumors may be traceable to underlying variation in DNA copy number." (Page 12698, col. 2). Accordingly, Pollack *et al.* confirm that genes that are amplified in at least one type of tumor are useful as markers for that type of tumor, and for prognostic uses directed to that type of tumor.

A *prima facie* case of lack of utility has not been established

Applicants respectfully submit that the Examiner has not made a proper *prima facie* showing of lack of utility, because the Examiner has not shown that Applicants' asserted utility is more likely than not incorrect.

The Examiner asserts that Haynes et al., Pennica, et al, Konopka, et al, Godbout, et al, and Li, et al. are no longer being relied upon to support the rejections. Nevertheless, the Examiner cites Hanna et al., Hittelman et al. and Hu et al. to support the assertion that "gene amplification data presented is not a reliable indicator of disease." (page 3 of the instant Final Office Action).

As a preliminary matter, Applicants reiterate that it is not a legal requirement to establish that gene amplification "necessarily" results in increased expression at the mRNA and

polypeptide levels. As discussed in the previous responses of record, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants have previously cited Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* as collectively teaching that in general, gene amplification increases mRNA expression. Applicants' arguments presented in the previously filed Responses are hereby incorporated by reference in their entirety.

Hanna *et al.*

The Examiner asserts that "Hanna et al. supports the rejection, in that Hanna et al. show that gene amplification does not reliably correlate with protein over-expression, and thus the level of polypeptide expression must be tested empirically." (Pages 7-8 of the instant Final Office Action).

Applicants respectfully submit that the Examiner appears to have misread Hanna *et al.* Hanna *et al.* clearly state that gene amplification (as measured by FISH) and polypeptide expression (as measured by immunohistochemistry, IHC) are well correlated ("in general, FISH and IHC results correlate well" (Hanna *et al.* p. 1, col. 2)). It is only a subset of tumors which show discordant results. Thus, Hanna *et al.* support Applicants' position that it is more likely than not that gene amplification correlates with increased polypeptide expression.

In contrast, in the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels.

Hu *et al.*

The Examiner has further cited Hu et al., in support of the assertion that "the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue." (Page 5 of the instant Final Office Action).

Regarding the art exemplified by Hu *et al.*, Applicants maintain their position that this reference still supports their case for the reasons outlined in their Preliminary amendment of July 5, 2005, which is hereby incorporated by reference. Briefly, Applicants maintain that, one of skill in the art should reach the conclusion, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly overexpressed, and that the present application discloses at least one patentable utility for the claimed PRO1153 polypeptides. Hu *et al.* did not look for a correlation between changes in DNA amplification and changes in mRNA and protein levels, and therefore their results are not contrary to Applicants' assertion that there is a correlation between the two. Applicants are not relying on any "biological role" that the PRO1153 polypeptide has in cancer for its asserted utility. Instead, Applicants are relying on the overexpression of PRO1153 in certain tumors compared to their normal tissue counterparts. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a diagnostic marker of cancer.

In summary, the Patent Office has failed to meet its initial burden of proof that Applicants' claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the cited articles do not provide sufficient reasons to doubt the statements by Applicants that PRO1153 has utility. As discussed above, the law does not require that DNA amplification is "always" associated with overexpression of the gene product. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

It is "more likely than not" for amplified genes to have incrased mRNA and protein levels

As discussed above and in detail previously, Applicants have provided ample evidence in the form of articles from the art, like Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and over a 100 references and Declarations by experts in the field of oncology and gene expression, i.e.: the Declarations by Dr. Audrey Goddard, Dr. Paul Polakis (I and II) and Dr. Avi Ashkenazi, to show that, in general, if a gene is amplified in cancer, it is "more likely than not" that the encoded protein will also be expressed at an elevated level.

The Examiner asserts that "[i]n order for PRO1153 polypeptide to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO1153 mRNA or PRO1153 polypeptide levels in lung tumors have been brought forth on the record." (Pages 4-5 of the instant Final Office Action).

The Examiner's reference to the lack of necessary correlation or accurate prediction in some of the rejections clearly shows that the Examiner again applies an improper legal standard when making this rejection. The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant. As discussed below, the references cited by the Examiner do not suffice to make a *prima facie* case that more likely than not no generalized correlation exists between gene (DNA) amplification and increased polypeptide levels.

In contrast, Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Applicants' Response filed June 25, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, as the Examiner has acknowledged, the art teaches that, in general, there is a correlation between mRNA levels and polypeptide levels.

Accordingly, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1153 gene, that the PRO1153 polypeptide is concomitantly overexpressed. Thus, the claimed PRO1153 polypeptide have utility in the diagnosis of cancer.

Applicants therefore respectfully request withdrawal of the rejections of Claims 119-126 and 129-131 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

II. 35 U.S.C. §112, first paragraph –Written Description

Claims 119-123 stand rejected under 35 U.S.C. §112, first paragraph, allegedly because the specification does not describe the claimed invention in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claims invention. (Page 10 of the instant Final Office Action).

In particular, the Examiner has taken the position that, while the specification provides adequate description for the polypeptide of SEQ ID NO:351, there is insufficient written description as to the identity of a polypeptide having at least 80% to 99% sequence identity to SEQ ID NO:1153. The Examiner has asserted that the polypeptide as encompassed with the broad definition of 80% to 99% identical to SEQ ID NO:351 are all required to practice the instantly claimed invention, and as stated in the previous office action, the specification does not provide an adequate written description of the broad genus having potentially highly diverse functions as encompassed by the phrase 80% to 99% sequence identity.

Applicants respectfully disagree.

Applicants maintain that, based on the ample disclosure in the specification, one skilled in the art would have known that Applicants had knowledge and possessed the claimed polypeptides with 80% to 99% sequence identity to SEQ ID NO: 351 whose encoding nucleic acids were amplified in lung tumors. The disclosed property of amplification of the encoding gene adds to the characterization of the claimed polypeptide sequences in a manner that one of skill in the art could readily assess and understand. As discussed previously, Applicants have recited structural features, namely 80% to 99% sequence identity to SEQ ID NO: 351, which are common to the genus. Applicants have also provided guidance as to how to make the recited variants of SEQ ID NO: 351, including listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides also have the functional activity "wherein the nucleic acid encoding said polypeptide is amplified in lung tumor." Example 170 of the present

application provided detailed protocols for the gene amplification assay. Accordingly, a description of the claimed genus has been achieved.

In the previously submitted Responses, Applicants relied on the holding of Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office in making the arguments that the written description requirement has been met. Applicants have submitted that the instant claims are very similar to the exemplary claim in Example 14 of the Synopsis of Application of Written Description Guidelines issued by the U.S. Patent Office. However, Applicants note that the PTO has recently issued a revised Training Manual for Written Description Guidelines, which provides the updated guideline in determining whether the written description requirement has been met. In order to more adequately conform to the new guidelines, Applicants submit herewith amendments to the claims removing the functional limitation from the claim language. Applicants respectfully submit that the instant claims are similar to the exemplary claim in Example 10 of the revised Training Manual on Written Description Guidelines issued by the U.S. Patent Office.

Example 10 of the Training Manual clearly states that the protein variants meet the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if: (1) the procedures for making such variant proteins is routine in the art, (2) the specification does not describe the complete structure or physical properties of the variants, although those skilled in the art would expect members of the genus to have properties similar to those of the reference sequence because of high degree of structural similarity, and (3) the variant proteins of the genus possess a significant degree of partial structure (see Claim 2 of Example 10).

Applicants submit that all the requirements in Example 10 are met for the variant polypeptides of Claims 119-123. In particular, Claims 119-123 require that the variant polypeptide of PRO1153 share a high sequence identity to SEQ ID NO:351. In addition, the procedures of making variant polypeptide of SEQ ID NO:351 are well-known in the art and described in detail in the specification. The instant specification includes extensive step-by-step guidance in the specification on how to make and prepare nucleic acids where the polypeptides have 80% to 99% identity to the polypeptide of SEQ ID NO: 351. For instance, the specification describes methods for the determination of percent identity between two amino acid sequences

(for instance see page 371, line 6, to page 375, line 9). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity. This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6). Accordingly, one of skill in the art could identify whether a variant PRO1153 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 371, line 6, to page 375, line 9) and methods of preparing the PRO polypeptides. (See page 375, line 11 and onward). Applicants claim only those polypeptides which meet the stated guidelines.

Therefore, Applicants submit that the specification provides ample guidance such that one of skilled in the art would know that Applicants possessed the invention as claimed in the instant claims, at the time of filing of the application. Accordingly, Applicants respectfully request reconsideration and reversal of this outstanding rejection under 35 U.S.C. §112, first paragraph.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **50-4634** Attorney Docket No.: **123851-181895 (GNE-2730P1C31)**.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: December 3, 2008

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